REMARKS

An Office action was mailed in the above-captioned application on September 26, 2006. Claims 6, 8-12, 21, 24, and 29-33 were pending in the application. Claims 6, 8-12, 21, 24, and 29-33 were rejected. This Amendment and Remarks document is submitted in response to said Office action. Claims 6, 9, 12, 21, and 24 have been amended, claims 31-33 have been cancelled, and new claims 34-36 have been added.

The Final Rejection

Where an examiner introduces a new ground of rejection that is neither necessitated by amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 C.F.R. § 1.97(c), a final rejection is not proper. M.P.E.P. § 706.07(a).

The Examiner asserts that Applicants' previous amendments necessitated the new grounds of rejection, and accordingly, that final rejection of the pending claims is appropriate.

In the previous Office action, a number of claims were rejected as being unpatentable over Willing, et al., *J Bone Miner Res*. 1998 Apr;13(4):695-705, and/or Uitterlinden, et al., *J Bone Miner Res.* 2001 Feb;16(2):379-85; however, Claim 6 was found to be free of this art. Claim 6 was amended to incorporate all of the limitations of the base claim, Claim 1, and intervening Claim 4, which were cancelled. Thus, Claim 6 as amended contains no additional elements as compared to original Claim 6. In the present Office action, Claim 6 is now rejected as being unpatentable over the combination Willing, et al. and Uitterlinden, et al. Applicants submit that the rejection of Claim 6 was not necessitated by the amendment of Claim 6, and that Claim 6 could have been rejected over the combination Willing, et al., and Uitterlinden, et al., in the first action.

Furthermore, Applicants note that the Examiner has cited new art, Warrell, et al., U.S. Pat. No. 4,529,593, and that a new ground of rejection is based on this reference. Applicants submit that the new ground of rejection was necessitated not by Applicants' amendments, but rather by the Examiner's discovery of the Warrell, et al., patent, since the current rejection of Claim 12 under 35 U.S.C. § 102(b) as being anticipated by Warrell, et al., U.S. Pat. No. 4,529,593, could have been made by the Examiner in any of claims 12-20 prior to the amendment of claim 12.

For these reasons, the finality of the Office action is improper and contrary to the M.P.E.P. Applicants request that the finality of the Office action be withdrawn.

The Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 6, 8-11, 21, 24, 29-31, and 33 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The second paragraph of Section 112 requires that the claims set out and circumscribe a particular area which applicants regard as their invention with a *reasonable* degree of precision and particularity.

Specifically, the rejection alleges that the recitation "the mammalian subject" in claim 6 renders claims 6, 8-11, and 29-31 indefinite as allegedly lacking in antecedent basis. This recitation has been amended to read "the subject." Additionally, claim 9 has been amended to recite "the subject" instead of "a subject." The recitation "the subject" has antecedent basis in "the female Caucasian subject" in Claim 6.

Claims 21, 24, and 33 have been rejected as allegedly being incomplete for omitting essential steps, such omission amounting to a gap between the steps. Claim 21 has been amended to recite that the method is a method of recommending a treatment regimen, and that the method comprises analyzing nucleic acid molecules of the subject to determine whether both said haplotypes are present in said subject, and providing a treatment regimen when both said haplotypes are present in said subject, wherein the treatment regiment is effective to decrease the risk of BMD-independent fracture.

In view of the foregoing amendments, reconsideration of the rejection under 35 U.S.C. § 112, second paragraph is respectfully requested.

The Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 6, 8-11, 21, 24, 29-31 and 33 under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of § 112 requires that a patent application be written so as to "enable any person skilled in the art to which it pertains . . . to make and use the same." A specification

is presumed to be enabling absent "a reason to doubt the objective truth of the statements contained therein." *In re Marzocchi*, 169 USPQ 367, 369 (C.C.P.A 1971). Further, a specification "may be enabling even though some experimentation is necessary," *United States v. Teletronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), so long as the amount of experimentation required is not "undue experimentation." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The test is whether the specification "provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Further, it is a tenet of patent law that an applicant need not teach what the skilled artisan already knows. Instead, it is preferred that an applicant "omit what is known in the art." *Hybritech Inc. v. Monoclonal Antibodies*, 231 USPQ 81, 94 (Fed. Cir. 1986).

Specifically, the rejection states that the claims are drawn to methods of determining "any" bone (fracture) susceptibility, methods of sampling "any" subjects, and methods of formulating "any" treatment regime. Applicants do not acquiesce in this rejection; however, in the interest of expediting prosecution, amendments have been made to address these concerns.

The independent claims, claims 6, 12, and 21, recite a Caucasian female subject. As noted above, claim 6 has been amended to recite "the subject" instead of "the mammalian subject," and claim 9 has been amended to recite "the subject" instead of "a subject." "The subject" refers to "the female Caucasian subject" in Claim 6. Thus, amended claims 6 and 9 do not refer to "any" subject.

Claim 21 has been amended to recite that the method is a method of providing a treatment regimen, and that the method comprises analyzing nucleic acid molecules of the subject to determine whether both said haplotypes are present in said subject to determine whether both said haplotypes are present in said subject, and providing a treatment regimen when both said haplotypes are present in said subject, wherein the treatment regiment is effective to decrease the risk of BMD-independent fracture. Claim 21 no longer refers to a method of formulating a treatment regimen based on a genotypic analysis, but rather method of recommending a treatment regimen to decrease the risk of bone mineral density (BMD)-independent fractures based on a genotypic analysis and risk factor, and it is believed that Claim 21 as amended is fully supported and enabled by the present specification.

Claims 6, 12, 21, and 24 have been amended replace the recitation "bone fracture" with "BMD-independent fracture." Support for this amendment can be found in the specification at, for example, page 6, lines 19-26; page 11, lines 8-14; and page 32, lines 13-20. Claims 6, 12, and 21 have been amended to recite that the VDR baT haplotype is a homozygous haplotype. The specification states at pages 30-31, that women homozygous for the VDR baT haplotype have a 2-fold and 10-fold increased risk for vertebral fractures when being heterozygous or homozygous for the estrogen receptor α haplotype px. (emphasis added). The claims now refer to the estrogen receptor α haplotype px and the homozygous VDR baT haplotype. Thus, the amended claims do not refer to determining "any" bone (fracture) susceptibility, but only to susceptibility to BMD-independent fracture or BMD-independent vertebral fracture, and specify the haplotypes for the estrogen receptor α gene and VDR gene.

Applicants submit that the claims, as amended, are fully enabled by the specification, and respectfully requests reconsideration of the rejection under 35 U.S.C. § 112, first paragraph.

The Rejection under 35 U.S.C. § 102(b)

The Examiner has rejected Claims 12 and 32 under 35 U.S.C. § 102(b) as being anticipated by Warrell, et al., U.S. Pat. No. 4,529,593. The Court of Appeals for the Federal Circuit has stated that anticipation requires the presence in a single prior art reference of each and every element of the claimed invention. *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1458 (Fed. Cir. 1984); *Alco Standard Corp. v. Tennessee Valley Auth.*, 1 U.S.P.Q.2d 1337, 1341 (Fed. Cir. 1986). "There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *Scripps Clinic v. Genentech Inc.*, 18 U.S.P.Q.2d 1001, 1010 (Fed. Cir. 1991) (citations omitted).

Specifically, the rejection states that Warrell, et al., teaches a method of treating bone fractures in a human individual comprising administering an effective amount of a pharmaceutically acceptable gallium compound, and that all patients responded to the treatment. The rejection reasons that Warrell, et al., teach a method applying to "any" human individual and that a population of any individuals includes individuals with genotypes px and baT.

Applicants respectfully traverse this rejection. Claim 12, as amended, requires determining whether the px haplotype of the estrogen receptor α gene and the homozygous baT

haplotype of the vitamin D receptor gene are present in said subject. Warrell, et al., does not teach determining whether the px haplotype of the estrogen receptor α gene and the homozygous baT haplotype of the vitamin D receptor gene are present in said subject. Warrell, et al., therefore, cannot anticipate Claim 12.

Claim 32 has been cancelled, rendering the rejection of Claim 32 moot.

Reconsideration is respectfully requested.

The Rejection under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 6, 9-11, and 29-31 under 35 U.S.C. § 103(a) as being unpatentable over Willing, et al., *J Bone Miner Res.* 1998 Apr;13(4):695-705, in view of Uitterlinden, et al., *J Bone Miner Res.* 2001 Feb;16(2):379-85. The Examiner bears the burden of establishing a *prima facie* case of obviousness (Section 103). In determining obviousness, one must focus on Applicant's invention as a whole. *Symbol Technologies Inc. v. Opticon Inc.*, 19 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1991). The primary inquiry is:

> whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have had a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be found in the prior art, not in the applicant's disclosure.

In re Dow Chemical, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), a combination of references must (1) disclose all the elements of the claim; (2) find a motivation to combine the references either in the references or in the art; and (3) have a reasonable expectation of success. Applicants submit the claims as amended are not obvious under this standard.

Specifically, the rejection states that Willing, et al., teaches an association in Caucasian women who were homozygous ppxx and lumbar spine and total bone mineral density, and that Willing, et al., teaches that low bone mineral density is a risk factor for osteoporosis and related fractures. The rejection also alleges that Willing,et al., teaches genotyping and amplification of the polymorphic *Pvu*II and *Xba*I sites followed by restriction digestion, but that Willing, et al., does not teach the use of vitamin D receptor gene sites of *Apa*I and *Taq*I.

Regarding Uitterlinden, et al., the rejection alleges that the reference teaches the interaction between VDR and susceptibility for fracture, including that the baT haplotype was overrepresented among fracture cases and can be used as a genetic marker for osteoporotic fracture.

The rejection reasons that it would have been *prima facie* obvious to modify the method of Willing, et al., to further include *Apa*I and *Taq*I taught by Uitterlinden, et al. The rejection reasons that Uitterlinden, et al., teaches that analyzing only the *Bsm*I RFLP can compromise the outcome of studies because heterogeneous groups are compared, that the haplotyping of three RFLPs, *Bsm*I, *Apa*I, and *Taq*I can accurately measure linkage disequilibrium at the 3' end of the VDR gene, and that the haplotypes can be used as markers for truly functional polymorphisms elsewhere in the 3' end of the VDR gene.

Applicants respectfully disagree with this rejection. Willing, et al. teaches that estrogen receptor genotypes are associated with lumbar spine and total body bone mineral density. More specifically, Willing, et al., teach that women who were homozygous pp or xx had low bone mineral density (p. 701, first column, text lines 13-15) (emphasis added), but does not teach an intereaction of the *Pvu*II and *Xba*I loci (as suggested in the rejection). Willing et al., also teach that women who were homozygous (–/–) at the *Pvu*II or *Xba*I loci (that is, PP or XX) had significantly different BMD levels according to their VDR status. (emphasis added). Specifically, Willing, et al., found an association between the estrogen receptor *Pvu*II genotype (–/–) (PP) and the VDR genotype at the *Bsm*I site. Women with *Pvu*II genotype (–/–) (PP) and bb VDR genotype had a very high average BMD, while individuals who had the (–/–) (PP) and BB VDR genotype had significantly lower BMD levels (abstract, p. 699, first column, Fig. 2 and accompanying text).

Willing, et al., notes that bone mineral density is an important risk factor for osteoporosis and related fractures. Such fractures are related to bone mineral density and can be described as BMD-dependent fractures; however, the risk of certain fractures is independent of bone mineral density. That is, a subject may have a normal (that is, no increased) risk of BMD-dependent fractures, but may still have an increased risk of fracture due to factors other than BMD. Such fractures can be described as BMD-independent fractures. Willing, et al. is silent as to the effect of estrogen receptor genotypes on susceptibility to fracture, and in particular BMD-independent fractures and vertebral fractures.

Uitterlinden, et al., teaches that more women who were heterozygous or homozygous for the baT haplotype had fractures than the women in the reference group, independent of bone mineral density. (abstract, p. 381, col. 2). Uitterlinden, et al., also teaches that the effect was the same for vertebral and non-vertebral fractures. (p. 381, col. 2).

As noted in the rejection, Uitterlinden, et al., teaches that analyzing only the *Bsm*I RFLP can compromise the outcome of studies. This is evident in Willing, et al., which teaches that the *Pvu*II and *Xba*I genotypes, in combination with the VDR genotype *Bsm*I genotype, have no consistent correlation with bone mineral density. (p. 701, p. 702, col. 2, first full paragraph).

The Examiner has not established a *prima facie* case of obviousness, because even if there is a motivation to combine Willing, et al., and Uitterlinden, et al., (which Applicants do not admit), there is no reasonable expectation of success with the combination. It is unclear what result would be obtained if the method of Willing, et al., is modified by Uitterlinden, et al. The effect the presence of the VDR haplotypes, if any, in combination with the various estrogen receptor genotypes (or haplotypes, since Willing, et al., is silent as to the effect of estrogen receptor haplotypes) cannot be ascertained from the references. The combined effect may or may not be correlated with low bone mineral density, since Willing, et al., (p. 701) teaches that the correlation of a particular estrogen receptor genotype (but not a haplotype) with low bone mineral density is population-specific, and Uitterlinden, et al., teaches that VDR haplotypes are not correlated with low bone mineral density, at least for non-vertebral bone density. The combined effect of VDR haplotypes with estrogen receptor genotypes may or may not be correlated with the frequency or type of fractures, since bone mineral density is only a risk factor for fractures (Willing, et al., p. 695) and the various VDR haplotypes may or may not be correlated with the type of fractures (Uitterlinden, p. 381). The combined effect may or may not be correlated with copy number of the alleles, since the estrogen receptor genotype that predicts high or low bone mineral density may be population specific (Willing, et al., p.701), and the effect of VDR haplotypes may or may not be dependent on copy number (Uitterlinden, p. 381). The results of the combination of Willing, et al. and Uitterlinden, et al., are therefore, unpredictable. Given this unpredictability, there would be no expectation of success in combining Willing, et al. and Uitterlinden, et al. to achieve the present invention.

The Examiner has also not established a *prima facie* case of obviousness, because, even assuming a motivation to combine the references, which Applicants do not admit, the combination of the references cited by the Examiner does not disclose all of the elements of the claimed invention. The present claims are directed to methods relating to susceptibility to BMD-independent fracture or BMD-independent vertebral fracture by determining the presence of a haplotype comprising the p and x alleles of the estrogen receptor α gene (whether homozygous

or heterozygous) and a homozygous haplotype comprising the baT alleles of the vitamin D receptor gene. Neither Willing, et al., nor Uitterlinden, et al., teach (1) determining either the heterozygous or homozygous px haplotype; (2) determining only the homozygous baT haplotype; or (3) associating the p and/or x genotype or haplotype with BMD-independent fractures or BMD-independent vertebral fractures. Applicants submit therefore, that the combination of Willing, et al., and Uitterlinden, et al. cannot render the present claims obvious.

Reconsideration is respectfully requested.

Closing Remarks

Applicant believes that the pending claims are in condition for allowance. If it would be helpful to obtain favorable consideration of this case, the Examiner is encouraged to call and discuss this case with the undersigned.

This constitutes a request for any needed extension of time and an authorization to charge all fees therefore to deposit account No. 19-1970, if not otherwise specifically requested. The undersigned hereby authorizes the charge of any fees created by the filing of this document or any deficiency of fees submitted herewith to be charged to deposit account No. 19-1970.

Respectfully submitted,

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